DETAILED ACTION

Status of claims

Claims 78-80, 88 and 90-97 are pending.

The amendment filed 5/26/11 which amends claims 78, 79 and 90, and cancels claims 84 and 85 has been entered. Claims 1-77, 81-83, 86, 87, 89, and 98-240 were canceled by the amendment filed 11/7/07. Claim 95 remains withdrawn from further consideration. Claims 78-80, 88, 90-94, 96 and 97 are examined in this Office action. The applicants' request (filled 5/26/11) for extension of time of three months has been entered.

Withdrawal of objections and rejections

[1] The 112/2 rejection of claims 79, 80, 84-85, 88 and 97-97 is withdrawn in light of the amendment of claims 79 and 90 and cancellation of claims 84 and 85. Yet, the following new 112/2 rejection is applied due to the current claim amendment.

[2] The objection of the specification is withdrawn in light of the amendment of the specification thereof.

[3] The 102 rejection of claims 78-80, 84 and 88 by Rothbard et al. is withdrawn in light of the amendment of the claim 78.

[4] The 103(a) rejection of claim 85 by Waugh et al. is withdrawn in light of the cancellation of claim 85.

[5] The 103(a) rejection of claim 85 by Rothbard et al. and Crowley et al. and Waugh et al. is withdrawn in light of the cancellation of claim 85.

IDS

The references cited in the information disclosure statement (IDS) filed 5/26/11, and the IDS filed 5/20/11 have been considered by Examiner.

Maintained-Objection to the drawings

The drawing filed 9/1/06 is objected to under 37 CFR 1.83(a) because of the following: It appears that drawing at page "8/12" (per the drawing set) lacks label as "Figure 8". Corrected drawing sheets in compliance with 37 CFR 1.121 (d) are required in reply to the Office action to avoid abandonment of the application. Any amended replacement drawing sheet should include all of the figures appearing on the immediate prior version of the sheet, even if only one figure is being amended. The figure or figure number of an amended drawing should not be labeled as

"amended." If a drawing figure is to be canceled, the appropriate figure must be removed from the replacement sheet, and where necessary, the remaining figures must be renumbered and appropriate changes made to the brief description of the several views of the drawings for consistency. Additional replacement sheets may be necessary to show the renumbering of the remaining figures. Each drawing sheet submitted after the filing date of an application must be labeled in the top margin as either "Replacement Sheet" or "New Sheet" pursuant to 37 CFR 1.121(d). If the changes are not accepted by the examiner, the applicant will be notified and informed of any required corrective action in the next Office action. The objection to the drawings will not be held in abeyance

New-Sequence Compliance

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. э 1.821(a)(1) and (a)(2). However, this application fails to **fully** comply with the requirements of 37 C.F.R. 1.821 through 1.825; Applicants' attention is directed to the final rulemaking notice published at 55 FR 18230 (May 1, 1990), and 1114 OG 29 (May 15, 1990).

In claim 78, the sequences of 4 peptides (except $(gly)_{n1}$-$(gly)_{n2}$, and $(gly)_{n3}$-$(gly)_{n4}$), disclosed without SEQ ID NO identification.

If the noted sequences are in the sequence listing as filed, Applicants must amend the specification to identify the sequences appropriately by SEQ ID NO. If the noted sequences are not in the sequence listing as filed, Applicants must provide (1) a substitute copy of the sequence listing in both computer readable form (CRF) and paper copy, (2) an amendment directing its entry into the specification, (3) a statement that the content of the paper and CRF copies are the same and, where applicable, include no new matter as required by 37 C.F.R. э 1.821 (e) or 1.821(f) or 1.821(g) or 1.821(b) or 1.825(d), and (4) any amendment to the specification to identify the sequences appropriately by SEQ ID NO.

Appropriate correction is required.

New-Objection to claims

Claim 78 is objected to because the purpose of the administration appears to be missing in the claim which is required to guide the skilled in the art to practice the claimed method.

New-Rejections - 35 USC § 112, first paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter rejection

Claims 78-80, 88, 90-94, 96 and 97 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement; this is a new matter rejection. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. The limitation of "...directly contact to form a non-covalent complex", which as amended into the claims on 5/26/11, is not supported in the specification as originally filed. Applicant can either cancel the new matter or point out specification support for the phrase in the specification as originally filed.

At page 10-11, the response filed 5/26/11 asserts that said limitation as to "directly contact" is supported by paragraphs [0029], [0045] and Figures 1 and 2 of instant specification, and argues that the absence of an intervening negative backbone component indicates a direct contact between the carrier and biologically active protein. This is not persuasive because none of [0029], [0045] and Figures 1 and 2 has provided sufficient description for the "directly contact to form a non-covalent complex". Although Figure 1 may show a contact between "therapeutic agent" (the biologically active protein) and the (positively charged) "carrier", said "contact" might be covalent or non-covalent or combination thereof, or might be through a component other than the component of the "carrier", i.e., indirect contact; and thus, this figure is not considered to have provided sufficient support for the limitation discussed above.

Scope of enablement

Claims 78-80, 88, 90-94, 96 and 97 are rejected under 35 U.S.C. 112, first paragraph, because while the specification may enable for a method of administering to a subject a "biologically active protein" which has been covalently or non-covalently attached to the and is capable of forming a complex (or a direct contact) with the positively charged carrier" wherein said "carrier" is HIV-TAT fragment has formula set forth in lines 15-18 of instant claim 18, e.g., $(gly)_p$-RGRDDRRQRRR-$(gly)_p$ wherein p has been defined in claim 78., does not reasonably provide enablement for the method discussed above but wherein said "positively charged carrier" is "an electric mimic" or "a steric mimic" of a polypeptide recited claim 78. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte Forman*, 230 USPQ 546(BPAI 1986). They include the nature of the invention, the state of the art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

(1) The scope of the claims/(2)The nature of the invention: Claim 78 and dependent claims therefrom as written are directed to a method of administering to a subject a "biologically active protein" which has been covalently or non-covalently attached to the and is capable of forming a complex (or a direct contact) with the positively charged carrier" wherein said

"carrier" is "an electric mimic" (genus) or "a steric mimic" (genus) set forth in claim 78, line 14. While at p[paragraph [0056] and [0057] the specification described the "electric mimic" and "steric mimic" and provided guidance thereof by citing reference incorporated at last line of page 21, the specification does not provide any factual indicia or example(s) as to making and using the "electric mimic" and "steric mimic" compounds to form a complex in which the biologically active protein directly contacts with the positively charged carrier and use the complex to administer to subject such as human (see page 19, line 12, the specification). Synthesis of the "electric mimic" and "steric mimic" compounds may not be routine. The art teaches that chemical synthesis of gem-diaminoalkyl compound which is an "electric mimic"/"steric mimic" compound (as set forth in the line 30, page 21, instant specification) is quite complicated and none of synthetic methods is successful in solution (see page 782, left col., last paragraph to right col., line 2, Fletcher et al. (*Chem. Rev.* (1998) 763-795), suggesting that make of the "electric mimic"/"steric mimic" compound may require non-routine experimentation. Therefore, in this case the scope of the claims is outside the realm of routine experimentation, and would have resulted in the necessity of undue experimentation.

(3) The unpredictability of the art: The level of the unpredictability of the art is high because of non-routine experimentation is required for the make of the "electric mimic" and "steric mimic" compounds discussed by reference Fletecher et al.

(4) The state of the prior art/(5)The quantity of experimentation necessary(6) The relative skill of those in the art: The specification fails to teach the correlation between the structure (the plurality of peptide(s)/protein(s) to be fused and/or unlimited numbers of the Tf mutations) and the function (enhancing plasma half-life of the fusion thereof). The relative art (US 20080020942

and Baker et al.) has suggested that Tf is susceptible to mutations and infeasible use of plurality of proteins for making fusion protein as it cause aggregation problem. Since the specification does not teach core domain(s)/sequence(s) critical for Tf maintaining "ability" of rendering fused protein(s)/peptide(s) stable (having increase half-life), identifying variant Tf molecules having said "ability" required a large quantity of experimentations even in the case that Tf fusion with one peptide or protein. The specification needs to provide sufficient guidance to be considered enabling for the claimed compositions (claims 1 and 45 and dependent claims therefrom).

The general knowledge and level of skill in the art do not supplement the omitted description with respect to how routinely make/synthesize the "electric mimic" and "steric mimic" compounds. The art teaches difficulties in synthesizing PMRI ("PMRI" stands for partially modified retro-inverso) peptides (see page 783, left col., lines 12-14, and page 764, left col., line 6, Fletecher et al.). It is of note that instant specification refers the "electric mimic" and "steric mimic" compounds to as PMRI peptide compounds by citing "Fletcher et al. reference at last line of page 21.Thus, this is evidence that the level of skill in this art is low relative to the difficulty of conducting said fusion.

In view of the preceding factors (1-5), the level of skill in this art is high and requires at least a peptide chemist and/or molecular biologist with several years of experience in protein synthesis and protein chemistry, and pharmacology (claim 24) as well as knowledge and technical skills in chemical modification of peptides/proteins and purification and drug formulation. Yet, even with a level of skill in the art as those mentioned in precedence, predictability of the results is still highly variable.

Reasonable correlation must exist between the scope of the claims and scope of the enablement set forth. In view of the quantity of experimentation necessary the limited working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would take undue trials and errors to practice the claimed invention. Thus, the amount and level of experimentation needed is undue.

New-Claim Rejections - 35 USC § 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter that the applicant regards as his invention.

Claims 78-80, 88, 90-94, 96 and 97 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 78 lacks antecedent basis for "the biologically active protein" (line 7) in the claim.

Claim 78 does not make it clear whether or not the limitation "*the biologically active protein is not modified by covalent attachment to a negatively charged backbone and positively charged carrier*" (lines 7-8) means that the "protein" contains no said "covalent attachment", or refers to an activity of said protein is not affected by said covalent attachment. Also, said limitation is unclear whether or not the "protein" is covalently attached to (i) the negatively charged backbone only, or (ii) both the negatively charged backbone and the positively charged carrier.

Claim 78 recites (lines 12-14) "wherein the positively charged backbone comprises a member selected from ... electronic mimic of a polypeptide and a strict mimic of a polypeptide". The recitation is unclear how the "backbone" (which is *a part* of the "positively charged carrier", see line 5, claim 78) can comprise the "polypeptide" (*entire* molecule)? It is of note that instant specification sets forth that the "positively charged carrier" is a polypeptide (see page 23, lines 21).

Claims 79, 80, 88, 90-94, 96 and 97 which depend from claim 78 are also rejected.

Maintained-Claim Rejections - 35 USC §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 78-80, 88, 90, 93, 94, 96 and 97 remain rejected under 35 U.S.C. 102(b) as being anticipated by Waugh et al. (WO0207773 A2).

Waugh et al. discloses delivery (administering) the therapeutic agent (see abstract, and p.4, lines 6-8) to a subject, wherein the agent (also called target agent, seepage 12) is covalently or non-covalently attached to a negatively-charged backbone (p.12, lines 12 and 13) and said agent is a therapeutic protein such as cytokines and hormones (p.12, line 27-28). The negatively-charged backbone attached therapeutic agent together with a "positively charged backbone" compound forms a non-covalent association complex (see p.3, lines 17-18 and 28-31, it is of note that the "biological agent" set forth at line 29 is the therapeutic agent" discussed above). Here, said non-covalent complex is considered to be equivalent to instant "*a non-covalent complex*" formed by a direct contact between "*positively charged carrier and* the *biologically active protein*" set forth in claim 78, lines 8-11.

The positively-charged backbone compound is a polypeptide comprising HIV-TAT fragment, e.g., $(gly)_p$-RGRDDRRQRRR-$(gly)_p$ (p is an integer from 0 to 20) (see p.9, lines 5-28) and has at least one efficiency group (see p.4, lines 2-3).

The administration route is transdermal (see p.18, line 33 to p.19, line 1, and Figures 3-10). Because functionality is an inherent property of a biomolecule, said composition must have greater transdermal delivery ability as compared to the agent in the absence of the attached efficiency group in the *"positively charged backbone compound"*. It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

These teach claims 78-80.

The preferred therapeutic agent is botulinum toxin (BOTOX) (see p.16, lines 1 and 14, and p.17, lines 7-8). Topical administration to skin and/or mucous membrane (equivalent to instant epithelium) is used (p.18, line 33-34, and p.19, line 4). The composition is administered via a sustained-release (see p.20, lines 21-26) route to skin which is considered to be equivalent to instant the face/surface of a subject administered (claim 96) or to mucous membrane i.e., inside mouth which is considered to be equivalent to instant to the subject other than the face /surface (claim 97) (see p.19, line 4). Thus, claims 88, 90, 96 and 97 are rejected.

Claim 93 is included in the rejection, because without setting forth specific structural limitation to the botulinum toxin polypeptide, the recombinant botulinum toxin is considered to have identical structure to native toxin thereof.

Waugh et al. teach that the botulinum toxin is a cosmeceutic agent as well, which anticipates claim 94.

The applicants' response to the above 102(b) rejection

At pages 14-18, the response filed 5/26/11 discusses the Waugh's section "Summary of the Invention", page 3, lines 28-29, and Figure 1 (p.15, last paragraph to p.17 last line), and asserts that Waugh et al. do not teach the composition comparing the biologically active protein (is not insulin) which is not modified by covalent attachment to negatively charged backbone nor teach the direct contact between the positively charged carrier and said protein as required by presently-amended claims (p.15, lines 5-14, and p. 17, last 5 lines). Thus, the response requests withdrawal of the rejection.

The applicants' arguments are found not persuasive because of the reasons set forth in the above rejection and the reasons below.

In the "Summary of Invention", Waugh et al. have disclosed a method of delivering to a subject the therapeutic agent (a biologically active "protein" such as cytokines or botulinum toxin both which are not insulin), wherein said "protein" (which has been covalently or non-covalently attached to the negatively charged backbone compound) forms "a non-covalent association complex" (see above) with the positively charged backbone compound (equivalent to instant "positively charged carrier" disclosed at line 9 of claim 78) as disclosed in page 3 of Waugh et al. and supported by Figure 1; this is consider to be equivalent to instant "*...positively charged carrier and biologically active protein directly contact to form a non-covalent complex*" in claim 78.

As far as the limitation "the protein is not modified by covalent attachment to negatively charged backbone" is concerned, bioactivity of the therapeutic protein (agent) of Waugh et al. is considered to remain upon its covalent modification via covalent attachment to the negatively charged backbone. It is of note that the limitation as written is ambiguously encompasses at least two possibilities: (i) in view of structure, the protein is not modified by the covalent attachment thereof, and (ii) in view of function, the protein's activity is not affected/modified by the covalent attachment. In this case, Waugh et al. have taught either case (i) or (ii). Thus, the rejection is proper and stands.

Maintained-Claim Rejections - 35 USC §103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* v. *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 78, 79, 80 and 90-92 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Waugh et al. (WO0207773 A3) in view of Aoki et al. (EP 1421948).

Waugh et al. discloses delivery (administering) the therapeutic agent (see abstract, and p.4, lines 6-8) to a subject, wherein the agent (also called target agent, seepage 12) is covalently or non-covalently attached to a negatively-charged backbone (p.12,lines 12 and 13) and said agent is a therapeutic protein such as cytokines and hormones (p.12,line 27-28). The negatively-charged backbone attached therapeutic agent together with a "positively charged backbone" compound forms a non-covalent association complex (see p.3, lines 17-18 and 28-31, it is of note that the "biological agent" set forth at line 29 is the therapeutic agent" discussed above). Here, said non-covalent complex is considered to be equivalent to instant "*a non-covalent complex*" formed by a direct contact between "*positively charged carrier and* the *biologically active protein*" set forth in claim 78, lines 8-11.

The positively-charged backbone compound is a polypeptide comprising HIV-TAT fragment, e.g., $(gly)_p$-RGRDDRRQRRR-$(gly)_p$ (p is an integer from 0 to 20) (see p.9, lines 5-28) and has at least one efficiency group (see p.4, lines 2-3).

The administration route is transdermal (see p.18, line 33 to p.19, line 1, and Figures 3-10). Because functionality is an inherent property of a biomolecule, said composition must have greater transdermal delivery ability as compared to the agent in the absence of the attached efficiency group in the *"positively charged backbone compound"*. It is of note that products of identical chemical composition cannot have mutually exclusive properties. A chemical composition and its properties are inseparable. Therefore, if the prior art teaches the identical chemical structure, the properties applicant discloses and/or claims are necessarily present. *In re Spada* 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). See MPEP 2112.01.

The above Waugh et al. teachings are applied to claims 78, 79 and 80.

The preferred therapeutic agent is botulinum toxin (BOTOX) (see p.16, lines 1 and 14, and p.17, lines 7-8), as applied to claim 90

Provided that Waugh et al. do not expressly teach the serotype or form of the botulinum toxin.

Aoki et al. teach different serotypes of the botulinum toxin (BT), e.g., serotype A (see abstract and Table 1) useful for relieve pain in a patient or treating a smooth muscle disorder by administering to said patient the BT polypeptide (see [0014]), and teach use BT derivative "BOTOX®" (see [0027], line 3), as applied to claims 91 and 92.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to choose suitable serotype of BT for certain therapeutic use. This is becasue the

structure and usefulness of said BT polypeptide including the BT derivative has been known in the art (see above) at the time instant application was filed, and because one of ordinary skill in the art, e.g., physician would have become more familiar with the use of the BT product disclosed by Aoki et al. and would have chosen appropriate BT molecule (see [0027]). Further, in view of feasible treatment of various disorders as set forth in Examples 1-11 by BT or by the BT derivative, one of ordinary skill in the art would have appropriately used certain BT serotype with reasonable expectation of success. Thus, the combination of the references' teachings renders the claims *prima facie* obvious in the absence of any unexpected results.

Examiner remark: the mention of the rejection herein of claims 78, 79, 80 and 90 has been set forth at page 10, lines 10-12 in the Office action mailed 11/26/10.

The applicants' response to the 103 rejection above

At pages 20 and 21, the response filed 5/26/11 argues that as discussed in the response to the 102 rejection, Waugh et al. do not teach the claimed method, and that, although Aoki et al. teach the serotypes or forms of botulinum toxin, Aoki et al. fails to supply the missing features in the Waugh's teachings; wherein the missing features are that the positively charged carrier (backbone) and the biologically active protein directly contact each other to form a non-covalent complex wherein the biologically active protein is not modified by covalent attachment to a negatively charged backbone. Accordingly, the response requests withdrawal of the rejection.

The applicants' arguments are found unpersuasive because, as discussed above, Waugh et al. have taught administration to a subject a therapeutic agent (biologically active protein) capable of forming a complex with a -charged backbone through the covalent or non-covalent attachment (form the complex) to said negatively-charged backbone wherein the bioactivity of said protein remain upon its covalent modification via covalent attachment to the negatively charged backbone which is without skill and knowledge of one of ordinary skill in the art (protein chemist). Thus, Waugh et al. teach instant claims 78, 79, 80 and 90 from which claims 91 and 92 (directed to particular botulinum toxin serotypes or derivatives) depend. Aoki et al. provide the teachings for said botulinum toxin serotypes, the motivation of combination of the references' teachings (Waugh et al. and Aoki et al.) has been discussed in detail in the above

corresponding sections; said combination renders claims 91-92 obvious. Thus, the 103 rejection is proper and stands.

Maintained-Provisional Rejection -Obviousness Type Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b). Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

[1] Claims 78-80, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 67-70 and 72 of Application No. 10591486 ('**486**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 67-70 and 72 of '486 disclose topically administering via transdermal route to a subject skin a bioactive protein which has therapeutic activity (e.g., botulinum toxins, claim 70 of '486) and is associated with a carrier that comprises a positively charged polypeptide containing the positively charged branching groups wherein said association between the protein

and the carrier is non-covalent. This is the common subject matter of instant claims 78-80, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the biological agent such as botulinum toxin, claim 94 is included in the rejection.

[2] Claims 78-80 and 90-94 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 28-30 and 33 of Application No. 12897188 ('**188**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 28-30 and 33 of '188 disclose a method for transdermally delivering a biological agent to a cell in a subject comprising administering to said subject a composition comprising (a) a positively charged backbone containing groups carrying a positive charge extending from the backbone (page 7, lines 14-16, the specification of '188), and (b) a biological agent having negatively charge, i.e., non-covalent interaction between (a) and (b); wherein the biological agent includes polypeptide such as growth hormone and botulinum toxin (BOTOX) (see page 15, lines 21-22 and 34-35, and page 16,line 14, the specification of '188); which is an obvious variation of instant claims 78-80 and 90-93.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the biological agent such as botulinum toxin, claim 94 is included in the rejection.

[3] Claims 78-80, 88, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 51-54, 64, 77, 78, 80 and 110 of Application No. 10591732 ('**732**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 51-53 of '732 disclose topically administering to skin or epithelium or face (claim 64 of '732) of a subject the botulinum toxin (BT) (e.g., serotype A, claim 80 of '732) or BT derivative or recombinant BT (claims 77 and 78 of '732) in conjunction with a positively charged carrier that comprises a positively charged backbone and branching groups, wherein the association between the carrier and the BT is non-covalent, which is the common subject matter of instant claims 78-80, 90-93, 96 and 97.

Claims 54 and 55 of '732 disclose the same subject matter as instant claim 94.

Claim 110 of '732 discloses a controlled release for the administration, which is the common subject matter of instant claim 88.

[4] Claims 78-80, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 9, 13-16 and 21-24 of Application No. 11816602 ('**602**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 9, 13-16 and 21-24 of '602 disclose treating wrinkles comprising administering to skin of a patient a formulation that comprises a botulinum toxin (BT), e.g., serotype A, or BT derivative "BOTOX®" see [0055] of '602), wherein the BT or BT derivative is non-covalently complexed with the positively charged backbone wherein said backbone further comprises positively charged efficiency groups (claims 13 and 21-24 of '602) equivalent to instant branching groups. This discloses the common subject matter of instant claims 78-80, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the BT ([0022], lines 11-13, '602), claim 94 is included in the rejection.

[5] Claims 78-80, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of Application No. 11954885 ('**885**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claim 15 of '885 discloses treating a disease by transdermally administering a conjugate to a target cell (i.e., a subject), wherein the conjugate comprises (i) a cargo molecule and (ii) a transport molecule wherein interaction between (i) and (ii) is non-covalent, wherein the transport molecule contains a positively charged polypeptide covalently attached to a positively charged backbone that is non-covalently bound to the cargo molecule (claims 1, 3 and 4 of '885); and wherein the cargo molecule is a therapeutic polypeptide such as a serotype of botulinum toxin (claims 11-13, of '885). The transport molecule has ability of increasing the penetration of the

cargo molecule through a biological membrane in the skin (claims 5 and 6 of '885) which is equivalent to effect of instant topical administration to the face or to a site other than the face of the subject as set forth in instant claims 96 and 97. These disclose the common subject matter of instant claims 78-80, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the BT, claim 94 is included in the rejection.

[6] Claims 78-80, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 15 of Application No. 12520964 ('**964**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claim 15 of '964 discloses treating a disease by transdermally administering a conjugate to a target cell (i.e., a subject), wherein the conjugate comprises (i) a cargo molecule and (ii) a transport molecule wherein interaction between (i) and (ii) is non-covalent, wherein the transport molecule contains a positively charged polypeptide covalently attached to a positively charged backbone that is non-covalently bound to the cargo molecule (claims 1, 3 and 4 of '885); and wherein the cargo molecule is a therapeutic polypeptide such as a serotype of botulinum toxin (claims 11-13, of '885). The transport molecule has ability of increasing the penetration of the cargo molecule through a biological membrane in the skin (claims 5 and 6 of '885) which is equivalent to effect of instant topical administration to the face or to a site other than the face of

the subject as set forth in instant claims 96 and 97. These disclose the common subject matter of instant claims 78-80, 90-93, 96 and 97.

Since "provide a cosmetic benefit to the subject" (instant claim 94) is considered to be inherent property of the BT, claim 94 is included in the rejection.

[7] Claims 78-80, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5 and 9 of Application No. 12647677 ('**677**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 1-5 of '677 disclose administering botulinum toxin (BT), e.g., serotypes A, in order to achieve a therapeutic or cosmetic effect to an individual in need thereof comprising injection) (a topical route) of a composition which comprises a positively charged carrier that contains a positively charged backbone with plurality of efficiency groups attached thereto, wherein said backbone is polyamino acid such as polylysine and wherein the efficiency groups are positively charged molecule such as $(gly)_{n1}$-$(arg)_{n2}$. BT can be derivative thereof such as "BOTOX®" (claim 9, of '677). These disclose the common subject matter of instant claims 78-80, 90-94, 96 and 97.

It is noted that page 25 of the response filed 5/26/11 requests abeyance of the obvious-type double patenting rejection until allowable subject matter is indicated. Note that no allowable subject matter can be indicated with a standing ground of rejection. Thus, it is suggested that applicant file the appropriate terminal disclaimer.

[8] (*New*) Claims 78-80, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-16 of Application No. 13141962 (‘**962**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 1-16 of ‘962 disclose administering botulinum toxin (BT), e.g., serotypes A (claim 2 of ‘962), in order to achieve a therapeutic or cosmetic effect to an individual in need thereof comprising injection) (a topical route) of a composition which comprises a positively charged carrier that contains a positively charged backbone with plurality of efficiency groups attached thereto, such as the efficiency group $(gly)_p$-RGRDDRRQRRR-$(gly)_p$ (claim 5 of ‘962). BT can be derivative thereof such as “BOTOX®” (claim 9 of ‘962). These disclose the common subject matter of instant claims 78-80, 90-94, 96 and 97.

[9] (*New*) Claims 78-80, 90-94, 96 and 97 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 and 16 of Application No. 13141935 (‘**935**). This is a provisional double patenting rejection because the conflicting claims have not in fact been patented. Although the conflicting claims are not identical, they are not patentable distinct from each other because of the reasons set forth below.

Claims 1-10 and 16 of ‘935 disclose administering botulinum toxin (BT), e.g., serotypes A (claim 2 of ‘935), in order to achieve a therapeutic or cosmetic effect to an individual in need thereof comprising injection) (a topical route) of a composition which comprises a positively charged carrier that contains a positively charged backbone with plurality of efficiency groups attached thereto, such as the efficiency group $(gly)_p$-RGRDDRRQRRR-$(gly)_p$ (claim 5 of ‘935).

BT can be derivative thereof such as "BOTOX®" (claim 9 of '935). These disclose the common subject matter of instant claims 78-80, 90-94, 96 and 97.

Examiner remark: the ODP rejections [8] and [9] above are not considered to hold finality shown below becasue both '962 and '935 are filed 6/23/11 while the last Office action is mailed 11/26/10.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a). A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Samuel Liu whose telephone number is (571)272-0949. The examiner can normally be reached on Monday-Friday, 9 am to 5:30 pro. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would

like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Samuel W. Liu/
Examiner, Art Unit 1656

/ANAND U DESAI/
Primary Examiner, Art Unit 1656
August 1, 2011